UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/584,020	11/08/2006	Simon Delagrave	20446-003US1	4729

26161 7590 06/02/2009
FISH & RICHARDSON PC
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
OGUNBIYI, OLUWATOSIN A	

ART UNIT	PAPER NUMBER
1645	

NOTIFICATION DATE	DELIVERY MODE
06/02/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/584,020	DELAGRAVE, SIMON	
	Examiner	Art Unit	
	OLUWATOSIN OGUNBIYI	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18,24-26 and 28-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18,24-26 and 28-30* is/are rejected.

7)☒ Claim(s) *26* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 June 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO AMENDMENT

The amendment filed3/26/09 has been entered into the record. Claims 1-17, 19-23 and 27 have been cancelled. Claims 18, 24-26 and 28-30 are pending and are under examination.

Rejections Withdrawn

The rejection of claim 27 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of the cancellation of the claim.

The rejection of claims 18, 24-30 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of the amendment to the claims and the cancellation of claim 27.

The rejection of claims 18 and 24-30 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is withdrawn in view of the amendment to the claims.

The rejection of claim 18 and 24-30 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendment to the claims.

The rejection of claims 18 and new claims 28-30 under 35 U.S.C. 102(e) as being anticipated by Lu et al (US 2004/0018487 A1 Jan. 29, 2004 now US patent 7,312,041 B2 Dec. 25, 2007) is withdrawn in view of the amendment to the claims.

Sequence Requirements

The specification and drawing are objected to because they contain sequence disclosure that is encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2 and thus fails to comply with the requirements of 37 C.F.R. § § 1.821-1.825 for the reasons below:

Amino acid sequences as used in § § 1.821 through 1.825

are interpreted to mean an unbranched sequence of four or more amino acids and should be identified by a sequence identifier (SEQ ID NO:).

Full compliance with the sequence rules is required in response to this office action.

Claim Objections

Claim 26 is objected to because the contains a sequence disclosure that is encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. § § 1.821-1.825 for the reason(s) set forth below:

Amino acid sequences as used in § § 1.821 through 1.825 are interpreted to mean an unbranched sequence of four or more amino acids and should be identified by a sequence identifier (SEQ ID NO:).

Full compliance with the sequence rules is required in response to this office action.

Rejections Based on Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 18, 24-26 and 28-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method of detecting the presence of a pathogen in a sample or disease of an organism in a sample from a diseased organism, said method comprising:
a) contacting a polypeptide with said sample, wherein said polypeptide comprises

an evolved PDZ domain having at least 95% identity with SEQ ID NO: 2, wherein said evolved PDZ domain binds to a target associated with said pathogen; and
b)detecting binding of said polypeptide to said target associated with said pathogen or disease in said sample.

The genus of polypeptides comprising an evolved PDZ domain with at least 95% sequence identity with the sequence of SEQ ID NO: 2 is large and comprises structurally variant species dues to the plethora of changes that can be made to the amino acid sequence of SEQ ID NO: 2. These changes include substitutions, deletions or insertions into up to 5% of the amino acid sequence of SEQ ID NO: 2. The claims require that members of said genus of variants have the ability to bind any target associated with *any* pathogen or *any* disease of *any* organism in a sample. The specification does not teach which 5% of the amino acid sequence of SEQ ID NO: 2 can be changed and still result in a protein that binds any target associated with *any* pathogen or *any* disease of *any* organism in a sample. The specification does not teach any PDZ variant that binds to any target associated with any pathogen or any disease state. The specification does not identify the common structure of the large genus of PDZ domain variants that enables said variant to retain binding to a target associated with a pathogen or a disease state. There is no disclosed correlation between a common structure of the genus of PDZ domain variants with the function of binding to a target associated with a pathogen or a disease state. The specification does not teach any engineered PDZ domain having up to 5% sequence variation with SEQ ID NO: 2 that binds to any target associated with a disease of an organism or any target associated with a pathogen including BclA of *B. anthracis* (or fragments thereof) or a polypeptide having a C –terminal sequence of EFYA or any targets from *Clostridium botulinum* with a dissociation constant of about 100 nM or lower; or a dissociation constant of about 15 nM or lower.

The written description requirement is separate and distinct from the enablement requirement (See also *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 920-23, 69 USPQ2d 1886, 1890-93 (Fed. Cir. 2004)) and adequate written description requires more than a mere reference to a potential method for producing and assaying engineered PDZ domain variants that binds to any target associated with a disease of any organism or any pathogen. The purpose of the written description requirement is broader than to merely explain how to 'make

and use' [the invention] *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1560, 19 USPQ2d 1111, 1114 (Fed. Cir. 1991) but the written description requires Applicants to have possession of the genus of PDZ domain variants that have at least 95% identity with SEQ ID NO: 2 that binds to any target associated with any disease or any target associated with any pathogen. The specification does not provide sufficient description for the large and variant genus of polypeptides comprising PDZ domain variants and associated targets such that one skilled in the art would envision what PDZ domain variant would bind particular targets associated with pathogens or associated with diseases of any organism, thus, Applicant was not in possession of said genus as of the time of filing.

2. Claims 18, 24-26 and 28-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

The facts that should be considered in determining whether a specification is enabling or if it would require an undue amount of experimentation to practice the invention include 1) the quantity of experimentation necessary to make or use the invention based on the content of the disclosure, (2) the amount of direction or guidance presented, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breadth of the claims. *In re Wands*, 858 F.2d 731, 735 (Fed. Cir. 1988). The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations. *In re Wands*,858 F.2d at 737, 8 USPQ2d at 1404. While the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, the factors that weigh more in making the instant enablement rejection are discussed below.

The nature of the invention

The claims are drawn to a method of detecting the presence of a pathogen in a sample or disease of an organism in a sample from a diseased organism, said method comprising:
a) contacting a polypeptide with said sample, wherein said polypeptide comprises an evolved PDZ domain having at least 95% identity with SEQ ID NO: 2, wherein said evolved PDZ domain binds to a target associated with said pathogen; and
b)detecting binding of said polypeptide to said target associated with said pathogen or disease in said sample.

The claims require the use of a polypeptide comprising evolved PDZ domain having at least 95% sequence identity with SEQ ID NO: 2 to bind any target associated with any pathogen or any disease, in a sample.

The breadth of the claims

The claims require the detection of the presence of any pathogen or disease of any organism in any sample by binding of the instant polypeptide to any target associated with said pathogen or disease. The scope of pathogens includes any microorganism or virus or prion causing disease in humans other animals or plants including but not limited to bacteria such as *Bacillus anthracis, Escherichia coli 0.157, Yersinia pestis, Helicobacter pylori, Clostridium difficile, Streptococcus pneumoniae, Staphylococcus aureus, Mycobacterium tuberculosis, Mycobacterium bovis, Clostridium botulinum, Clostridium tetani* and the like. Viral pathogens include, for example, human immunodeficiency viruses (HIV), hepatitis A, B and C viruses, (HAV, HBV, HCV), respiratory syncytial virus (RSV), poliovirus, Coxsackievirus A9 AV9), smallpox virus, CMV (cytomegalovirus), flaviviruses, papillomaviruses, coronaviruses (e.g., SARS-CoV), influenza virus, viral plant pathogens such as alfalfa mosaic virus, tobacco mosaic virus, and the like. Other microbial pathogens include parasites and fungi such as, for example, *Plasmodium falciparum* (malaria) and the fungus *Candida albicans*, respectively, and the like. Prion pathogens include transmissible spongiform encephalopathies such as bovine spongiform encephalopathy (BSE), Creutzfeld-Jacob disease (CJD) and the like. See specification p. 13-14. The scope of disease includes but are not limited to any of numerous pathological conditions of the mind or body. The disease state can be infectious or non-infectious. The disease state can be symptomatic or non-symptomatic infection by a pathogen. The disease state can be chronic or acute, and also includes abnormal immune

responses (e.g., allergies). Example disease states include pathogen infection or toxicity due to exposure to pathogen-related toxins such as bacterial (e.g., botulism, anthrax), fungal, or viral infection. Further, example disease states include non-infectious diseases such as cancers (prostate, breast, etc.), cardiopulmonary diseases (myocardial infarction, atherosclerosis, etc.), neurodegenerative diseases (Alzheimer's, Parkinson's, ALS, etc.), allergic responses (e.g., asthma, hives, etc.) and the like. See specification p. 11.

The specification also broadly defines target as any molecular entity to which a further molecular entity binds. Thus, this includes, DNA (single and double stranded), RNA, and proteins– any molecular entity associated with a pathogen or disease to which another molecular entity can bind. See p. 11-12.

The amount of guidance or direction presented and The State of the Prior Art

The specification refers to an evolved PDZ domain that has been subject to directed evolution or other in vitro evolution techniques (p. 7 lines 26-33. p. 10 lines 13-31). The specification teaches that SEQ ID NO: 2 is the PDZ domain of hCASK i.e. human CASK protein (p. 7 line 36). The specification contemplates a wide variety targets associated with a large number of disease states or pathogens to be detected including allergies (IgE, IL-5, Il-17), IgA, IgD, IgM or IgG), cytokines, beta 2 macroglobulin, cancers e.g. prostate specific antigen, Alzheimer's (amyloid beta protein), bacterial and viral and fungal proteins etc (see specification p. 11 lines 12-27 to p.13 lines 1-6).

The specification teaches how to evolve hCASK PDZ domain (SEQ ID NO: 2) in vitro and teaches how to select variant mutants that are capable of recognizing a peptide of the sequence of SEQ ID NO: 26 of *Bacillus anthracis* BclA protein. See example 10. However, the specification does not disclose which variant of SEQ ID NO: 2 bound this peptide and do not disclose whether the selected variants are 95% identical to SEQ ID NO: 2.

The specification does not correlate the generation of variants of SEQ ID NO: 2 that are 95% identical to SEQ ID NO: 2 with the detection of the presence of any pathogen or the presence of any disease of any organism in any sample. The specification does not provide guidance as to the instant PDZ evolved variants wherein said polypeptide binds to said target

with a dissociation constant of about 100 nM or lower; or a dissociation constant of about 15 nM or lower or wherein the target is EFYA.

The art teaches that PDZ hCASK domain binds to the c-terminal EFYA amino acid sequence of synedecans which are cell surface heparan sulfate proteoglycans taught to act as extracellular matrix receptors (Cohen et al. The Journal of Cell Biology 142: 129-138, 1998, cited in IDS). Example 10 of the specification teaches screening variants of SEQ ID NO: 2 for binding to SEQ ID NO: 26 which corresponds to the C-terminus of protein BclA found in the exosporium of *Bacillus anthracis* spores but does not disclose particular variants that are 95% identical to SEQ ID NO: 2.

The specification does not teach which other targets associated with the breadth of targets associated with a pathogen or the breadth of targets associated with a disease that contain the c-terminal EFYA amino of synedecans or SEQ ID NO: 26.

Unpredictability/unpredictability of the Art

Furthermore, the art teaches that PDZ domains interact with other proteins to participate in protein-protein interactions (Skelton et al. The Journal of Biological Chemistry 278:7645-7654, cited in IDS p. 7645 introduction). Thus, it is unpredictable that evolved PDZ domain having at least 95% identity with SEQ ID NO: 2 (including SEQ ID NO: 2) will bind to non-protein targets associated with a pathogen or associated with a disease of an organism as claimed and the specification does not provide guidance to the contrary. Thus, it is unpredictable that the prophetic example of detecting *B. anthracis* protein BclA by binding of PDZ variants to the C terminus of BclA (SEQ ID NO: 26) can be extrapolated to the entire scope of the instant claims i.e. detecting any pathogen or disease in a sample.

The quantity of experimentation necessary to make or use the invention based on the content of the disclosure

While, the specification teaches how to evolve SEQ ID NO: 2, the specification has not sufficiently taught how to use the evolved PDZ domain having at least 95% identity with SEQ ID NO: 2 to detect any pathogen in a sample or any disease of any organism in a sample. The specification does not teach the structural features of an evolved PDZ domain having at least 95% identity with SEQ ID NO: 2 that is able to detect all pathogens or all diseases of an organism by binding to all targets associated with pathogens or diseases. Furthermore, a large

quantity of experimentation would be required to screen all targets associated with all pathogens and all diseases for which one comprises EFYA or SEQ ID NO: 26 to which the instant PDZ variants including SEQ ID NO: 2 are proposed to bind.

Even though compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed and example may be "working" or "prophetic", based on the analysis of the pertinent factors disclosed above, undue experimentation would be required of the skilled artisan to use the invention commensurate with the scope of the claims. It is unpredictable that the prophetic example of detecting *B. anthracis* protein BclA by binding of PDZ variants to the C terminus of BclA (SEQ ID NO: 26) can be extrapolated to the entire scope of the instant claims i.e. detecting any pathogen or disease in a sample. Moreover, in the prophetic example, there is no disclosure as to the structure of the PDZ variants i.e. whether they are 95% identical to SEQ ID NO: 2 and also no disclosure as to which variant binds with a dissociation constant of 100 nM or lower or 15 nM or lower. If little is known in the prior art about the nature of the invention (i.e. method of detecting the presence of a pathogen in a sample or disease of an organism using evolved PDZ domain having at least 95% identity with SEQ ID NO: 2 that binds to any target associated with any pathogen or any disease of an organism) and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. >See, e.g., *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004) ("Nascent technology, however, must be enabled with a specific and useful teaching.' The law requires an enabling disclosure for nascent technology because a person of ordinary skill in the art has little or no knowledge independent from the patentee's instruction. Thus, the public's end of the bargain struck by the patent system is a full enabling disclosure of the claimed technology." (citations omitted)).< In view of the above analysis, undue experimentation would be required to use the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 18, 24-26 and 28-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are drawn to a method of detecting the presence of a pathogen in a sample or disease of an organism in a sample from a diseased organism, said method comprising:
a) contacting a polypeptide with said sample, wherein said polypeptide comprises an evolved PDZ domain having at least 95% identity with SEQ ID NO: 2, wherein said evolved PDZ domain binds to a target associated with said pathogen; and
b)detecting binding of said polypeptide to said target associated with said pathogen or disease in said sample.

Claim 18 is confusing because how can the PDZ domain be evolved and also be 100% identical (the claims recite at least 95% identity which includes 100%) to SEQ ID NO: 2? The specification teaches an evolved PDZ domain describes a PDZ domain that is the product of an *in vitro* evolution process of the parent PDZ domain. See p. 11 lines 1-7. Thus, a PDZ domain that is 100 % identical to SEQ ID NO: 2 cannot be 'evolved' as it is identical to the parent PDZ domain.

Status of Claims

Claims 18, 24-26 and 28-30 are rejected. Claim 26 is objected to. No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to OLUWATOSIN OGUNBIYI whose telephone number is 571-272-9939. The examiner can normally be reached on M-F 8:30 am- 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Robert B Mondesi/
Supervisory Patent Examiner,
Art Unit 1645

/Oluwatosin Ogunbiyi/
Examiner, Art Unit 1645